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Two-part device for the controlled delivery of an active ingredient

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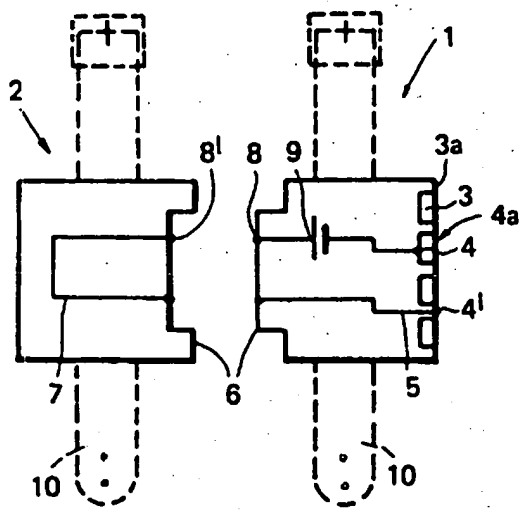

FIG. 1a

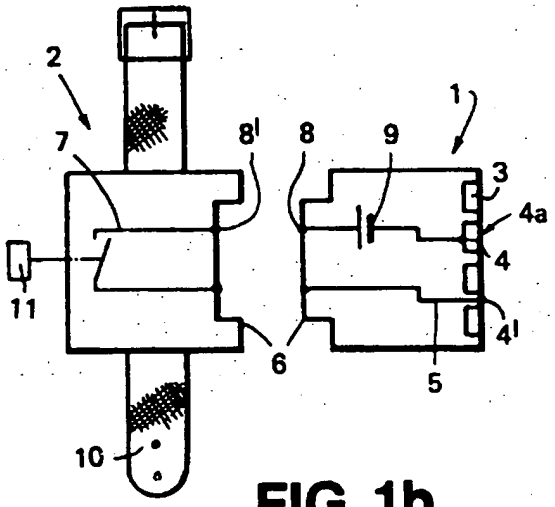

FIG. 1b

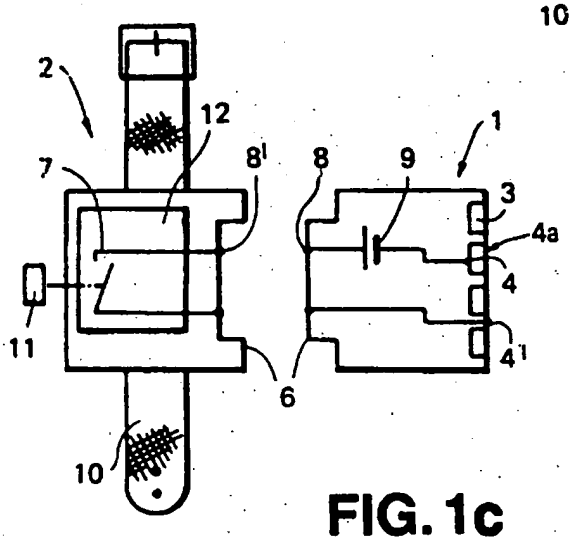

FIG. 1c

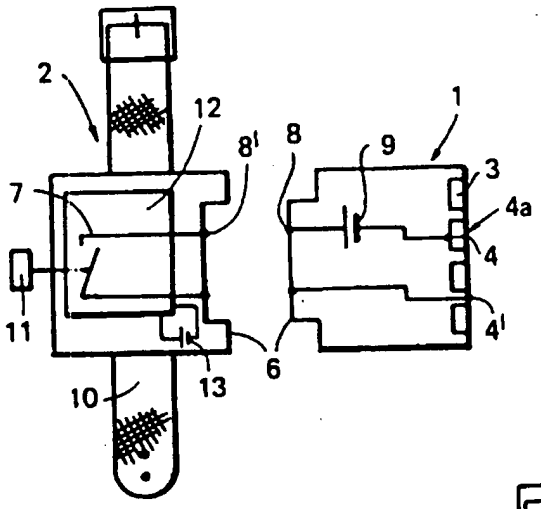

FIG. 1d

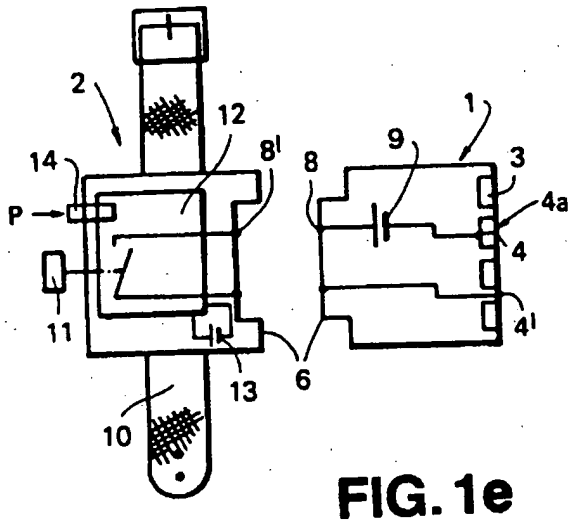

FIG. 1e

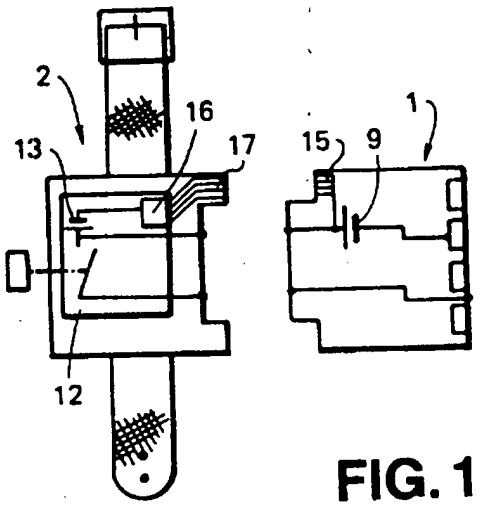

FIG. 1f

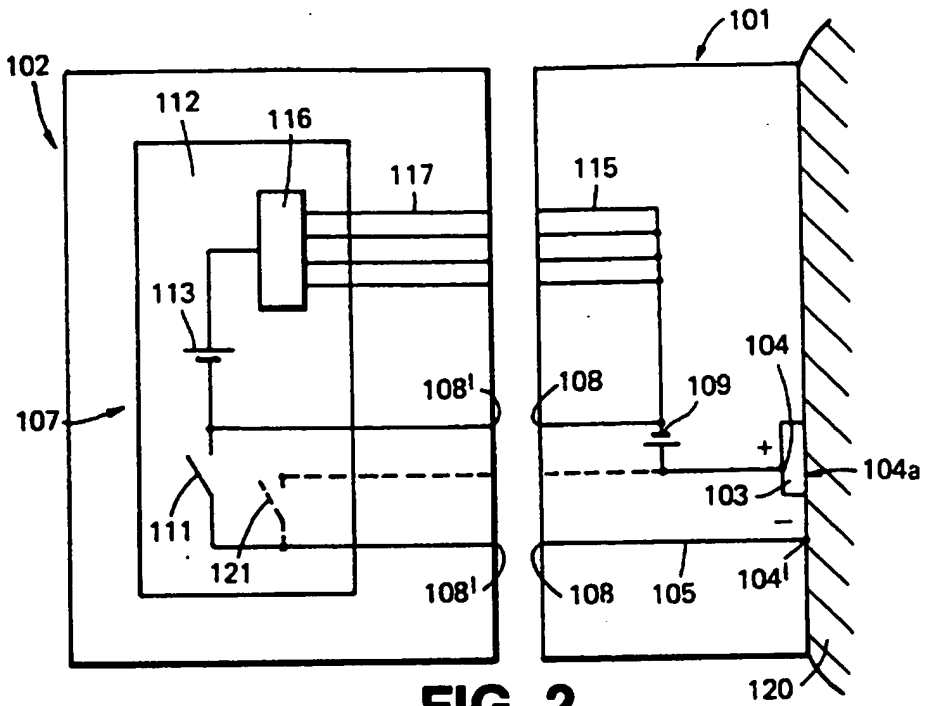
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FIG. 2

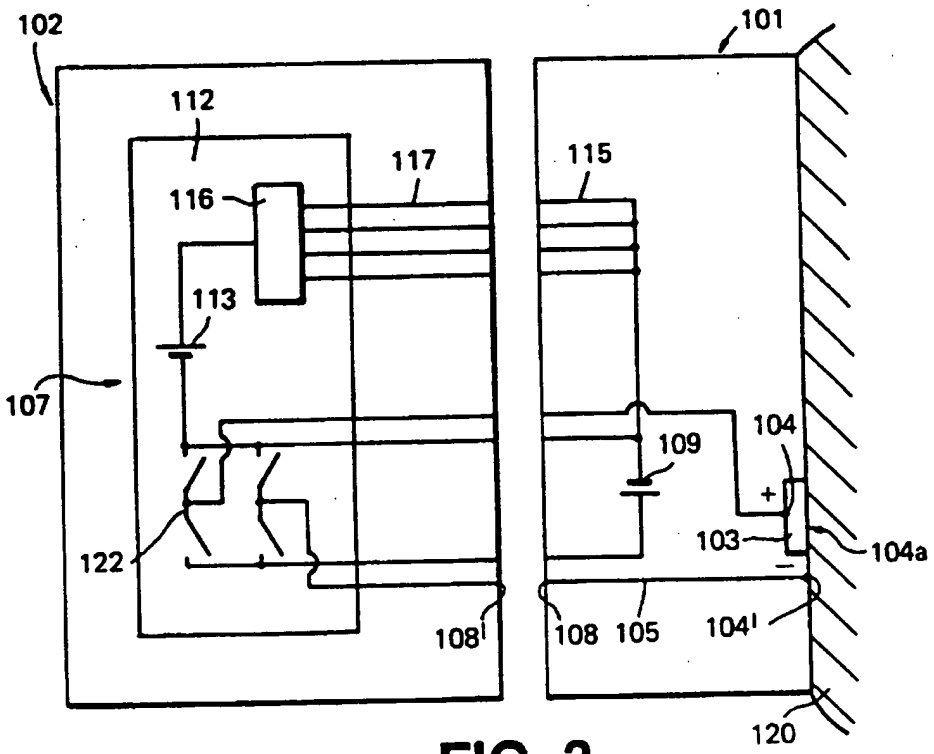
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FIG. 3

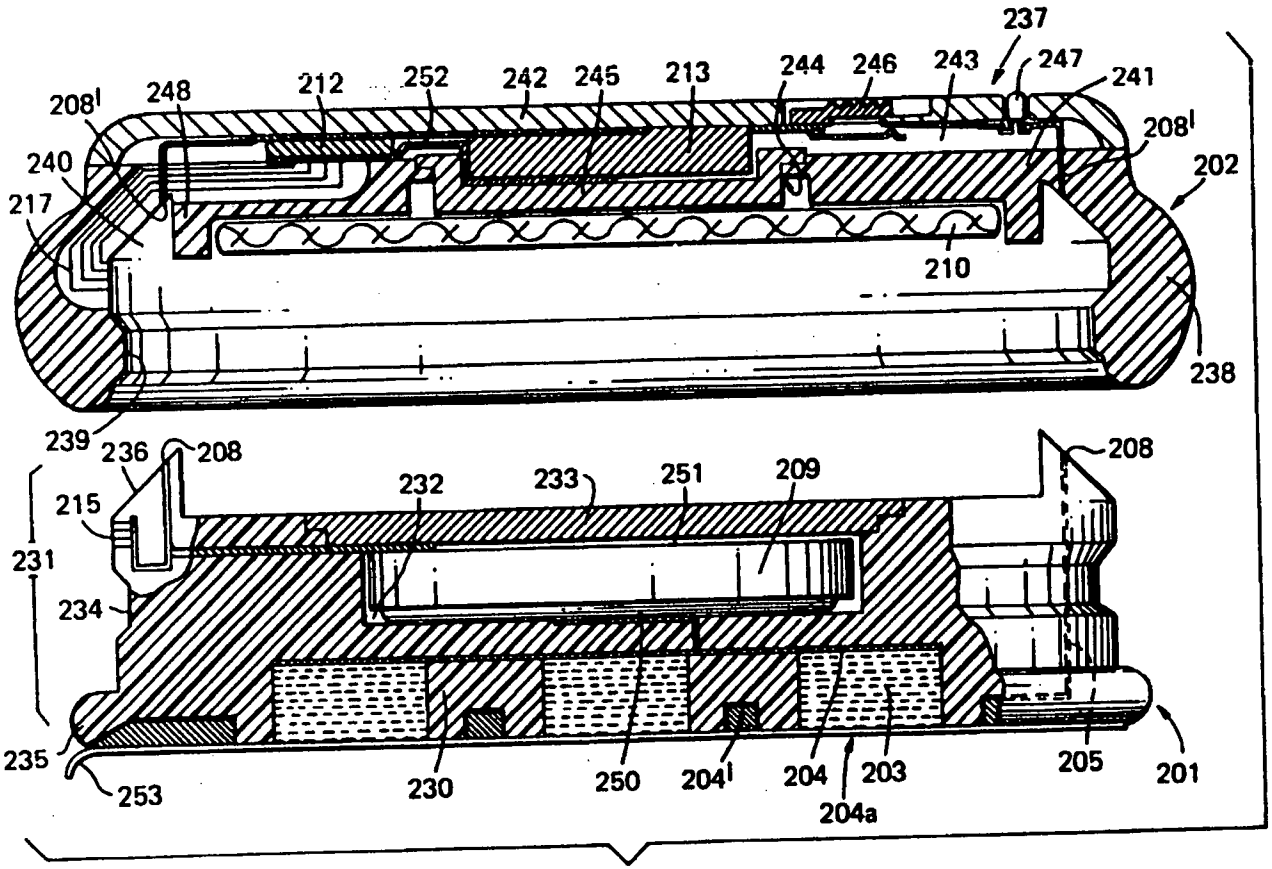
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FIG. 4

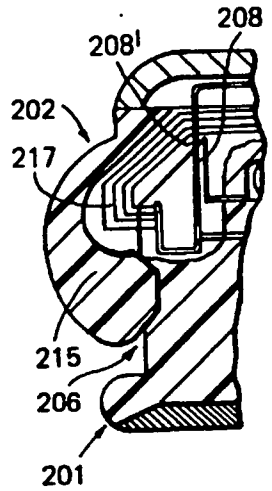
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FIG. 5

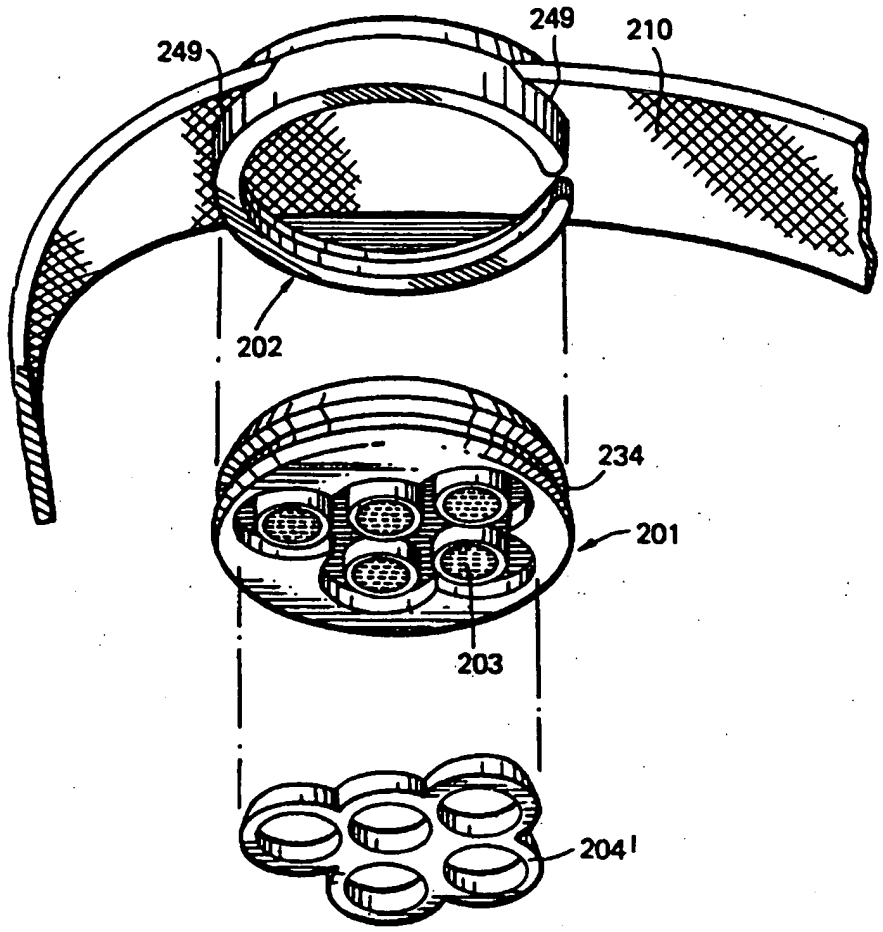

FIG. 6

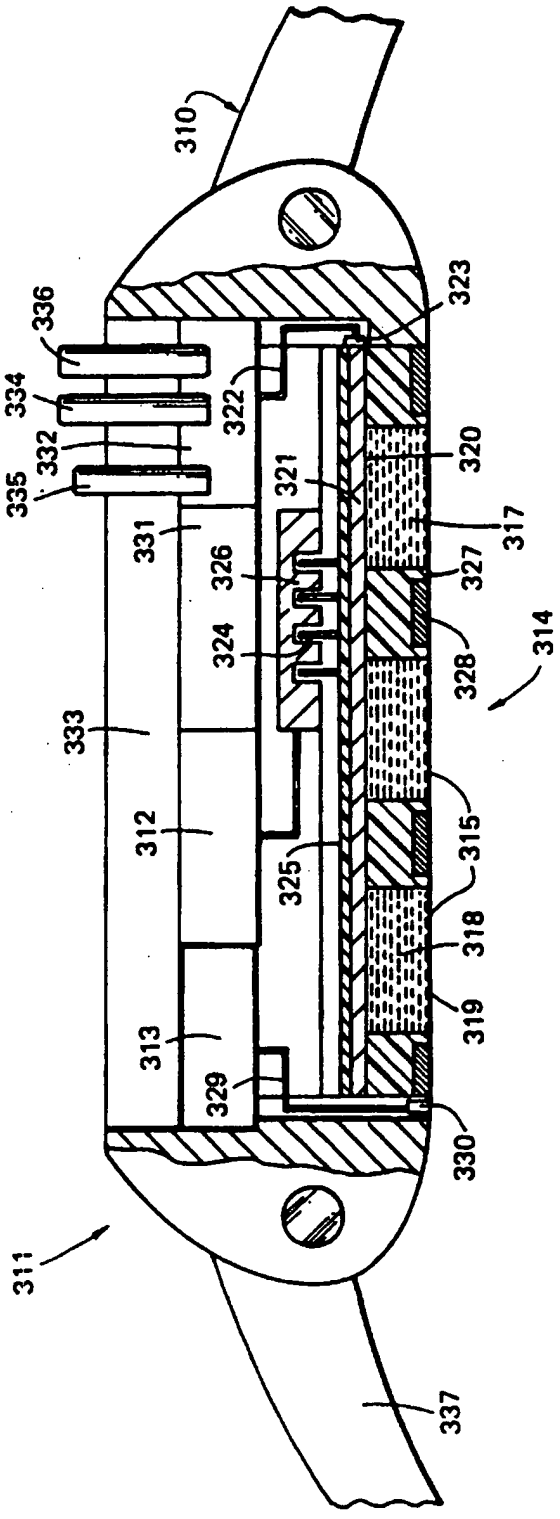
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FIG. 7

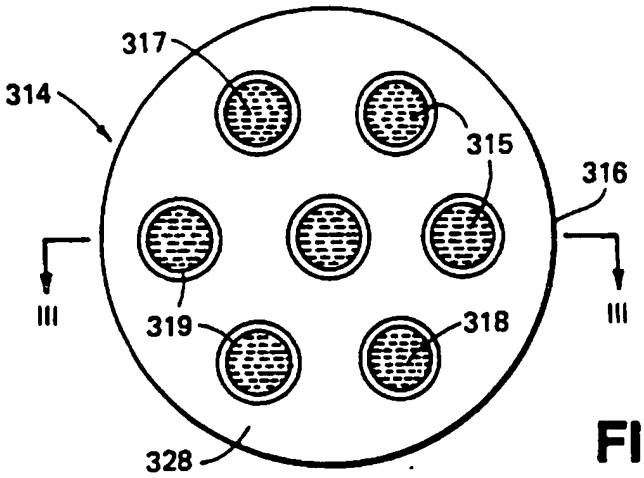

FIG. 8

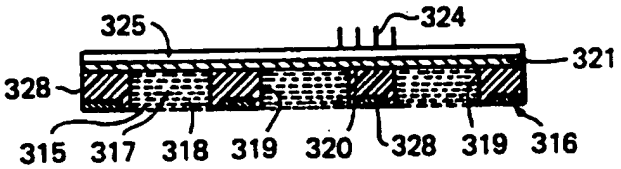

FIG. 9

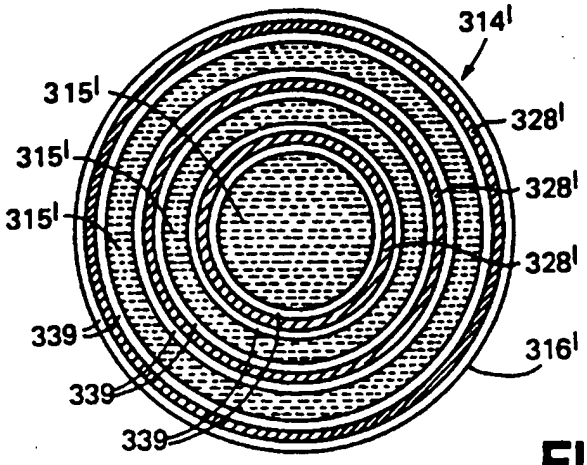

FIG. 10

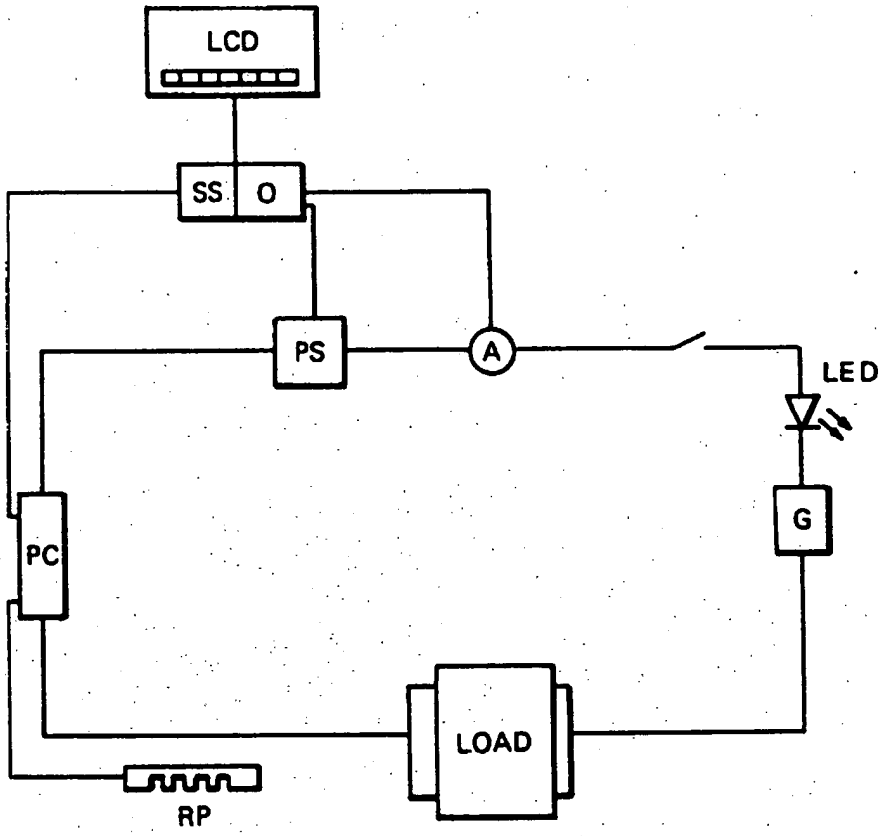

FIG. 11

TWO-PART DEVICE FOR THE CONTROLLED DELIVERY OF AN ACTIVE INGREDIENT

This invention relates to a two-part device for the controlled delivery of an activ ingredient to the skin under the influence of an iontophoretic or electro-osmotic force.

The technique of iontophoresis has been used on a limited scale in medical therapy. Iontophoresis is the process of moving ions into surface tissues with the aid of an electrical current. The technique was discovered nearly a century ago, but it is only in recent years that much interest has been shown in it as a method of local drug administration of ions; its chief proponents are to be found in the disciplines of dermatology, dentistry and otolaryngology. It is a safe, well documented method of introducing ions or polar substances into the skin by the application of a direct current between two electrodes placed on the skin of the patient. One advantage claimed for iontophoresis as a technique for drug administration is that systemic toxicity is virtually eliminated, since only a small amount of drug is delivered. (Gangarosa L.P. et al. (1978) J. Pharm. Sci., 67, 1439-1443).

Iontophoretic devices are known from our sister company's EP-A 0 252 732, and from EP-A 0 060 451, EP-A 0 058 920, GB-A 2 104 388, New Zealand Patent Specification No. 184,551 and U.S. Patent Specification Nos. 4,474,570, 4,557,723, 4,622,031 and 4,731,049. One problem encountered with many such known iontophoretic devices concerns the battery power/size ratio for batteries used to operate such devices. In order to keep such devices of reasonable dimensions for use in the administration of active ingredient to at least ambulatory subjects being treated, the battery must be relatively small. However, the power requirements of such devices when actively delivering active ingredient are such that the battery has a relatively short life span.

It is envisaged that many drugs will require quite different delivery programs when administered by the iontophoretic route. Thus for effective therapy some drugs will require slow continuous delivery over relatively long periods of time, for example 12 hours or more, while other drugs will require delivery for 20 min. every 8 hours or so, or perhaps as infrequently as every 3 days. Thus calcitonin for use in the treatment of osteoporosis would suitably be administered once every three days. In order to cover all such treatment regimens, it would not be practicable to leave it up to a patient or, indeed, a doctor or pharmacist to set up the device on each occasion to match the required delivery program.

When iontophoretic devices are applied to the skin, burns often occur. These burns result from the fact that the voltage supplied by the generator is not adapted to the patient, or because the active ingredient diffuses too rapidly or in doses that are too strong, or because the electrode is not correctly applied to the skin.

To prevent a current that is not very well adapted to the patient being supplied by the source of energy and causing burns, U.S. Patent Specification No. 4,725,263 discloses a device that permits the setting of several values for the supplied current intensity. This device comprises two parts, an electrode and counter electrode module also containing medicament reservoirs, and a control module comprising an electric circuit with several conductors which can be selectively broken in order to determine the number of intensity units of the current supplied.

This device, however, does not allow the intensity of the current supplied to be regulated accurately as a function of the type of medicament and/or patient. It is therefore not possible to exclude the risk of burns completely. Furthermore, when one of the conductors has been broken, the value of the current is

determined definitively. In order to obtain a different value it is thus necessary to employ a second control modul . This device is consequently fairly costly to use.

It is an object of the present invention to provide a device for the controlled delivery of an active ingredient to the skin under the influence of an iontophoretic or electro-osmotic force which overcomes the aforementioned disadvantages of known iontophoretic devices.

It is a further object of the present invention to provide a device for the controlled delivery of an active ingredient to the skin under the influence of an iontophoretic or electro-osmotic force which can be programmed to deliver a multiplicity of active ingredients according to selected delivery programs.

Accordingly, the invention provides a two-part device for the controlled delivery of an active ingredient to the skin under the influence of an iontophoretic or electro-osmotic force, comprising a reusable first part housing a programmable controlling member and an electrical circuit having overriding means whereby a subject can activate the device to deliver active ingredient at other than a pre-set time up to a predetermined maximum number of such activations, and a disposable and replaceable second part comprising an electrode unit containing said active ingredient and having at least one active electrode and a counter electrode, said at least one active electrode being disposed in, surrounded by, but isolated from, a skin-contacting surface defining said counter electrode, said second part being engageable with said first part in a manner so as to select a program applicable to said active ingredient, and said program when activated bringing about the controlled delivery of active ingredient from the electrode unit to the skin, the disposable and replaceable second part housing an associated power source for delivery of said active ingredient.

As used herein the term active electrode comprises electrically conductive material, a reservoir and medium containing the active ingredient.

Thus the first part of the two-part device according to the invention contains the microelectronics and memory necessary to

perform a multiplicity of different drug delivery schedules and the s cond part which is engageable with the first part in such a manner that it indicates to th first part what drug is contained in the second part and how it should be delivered, has an associated power source which supplies the power to deliver the active ingredient through the skin from the electrode unit. The power source will suitably comprise conventional miniature or "light-weight" batteries. For example, conventional sheet batteries and microbatteries may be used. Suitable batteries are alkaline batteries and lithium batteries of the type used in hearing aids and watches. The use of lithium batteries has the additional advantage that in spite of the fact that the second part is discarded after use, the environment does not suffer any pollution as a result.

The second part of the device thus contains two consumable elements (the active ingredient and a power supply), which normally have to be replaced after a given period of use (24 hours, for example). On the other hand the first part contains control means in the controlling member which are costly and not consumable and which, in contrast, must be able to be used numerous times. Consequently, not only is the device according to the invention much less expensive to use because only the consumable part of it is replaced, but it is also very convenient for a patient who is not medically trained to use because the adjustment of the control means does not have to be reset by a specialist each time the second part is replaced.

For pharmaceutical stability and other reasons, the electrode unit can be replaceable as required such as every day or every week. In some instances, depending on the stability of the active ingredient, it may be desirable to have the electrode filled with active ingredient by either the pharmacist prior to dispensing or the patient prior to use.

The second part preferably comprises a plurality of spaced-apart and isolated active electrodes arranged on the skin-contacting surface. The plurality of electrodes may be concentrically arranged and spaced-apart by means of an insulating material.

Such an arrangement of a plurality of electrodes is found to facilitate delivery of active ingredient by minimizing current requirements for such delivery as well as minimizing any skin irritation associated with the use of the device.

The second part of the device is adapted to engage with and affix to the first part in any suitable manner such as by clipping, snap-fit screwing, wedging, bayonet-joint or otherwise securing the respective parts together, such that the skin-contacting surface of the second part is adjacent to and contactable with the skin when the device is attached to a limb or elsewhere on the body of a subject to be treated in use.

On a second surface of the second part remote from said skin-contacting surface, the second part is provided with mechanical or electrical contact means adapted to select a program applicable to the active ingredient contained in the or each active electrode, which the programmable controlling member identifies as containing the or each active ingredient and which said controlling member thus recognises should be administered according to a prescribed regimen.

According to one embodiment of the invention the first and second parts have one or more co-operating electrical contact(s) which on engagement of the respective first and second parts select a given program.

The second part may select a given program by means of a bar code readable by said first part. Preferably, once said second

part engages said first part it is moved relative thereto enabling said bar code to be scanned by a light source in said first part.

According to a second embodiment of the invention said second part has one or more projection(s) engageable with one or more co-operating aperture(s) in said first part, the or each aperture housing a microswitch which is activated on engagement of the parts to select a given program.

Preferably, the electrical circuit includes means for indicating an active ingredient is being actively delivered. This feature is desirable for example to reassure the subject being treated that he or she is receiving the prescribed active ingredient.

The electrical circuit may also include means for indicating that a power source has failed or weakened.

Preferably in circumstances where the device is not worn continuously, the electrical circuit includes alarm means to alert a subject when it is time for the active ingredient to be delivered. Such alarm means will suitably comprise a timing circuit which will give a bleep which will prompt the user to apply the device to the body.

The first or second part preferably includes means for activating the program when said first and second parts are in the engaged position. The means for activating the program may be an ON/OFF switch. In a preferred embodiment the ON/OFF switch is activated to the ON position only when the device is <u>in situ</u> on the body of a subject to be treated. The ON/OFF switch may be activated to the ON position by pressure exerted by an attachment means when affixed to the body of said subject.

The electrical circuit suitably includes means for monitoring and indicating the content of the active ingredient in the device. The inclusion of such means would alert a subject undergoing a treatment regimen using the device if the content of active ingredient was not present in an amount effective for a given treatment. For example, the presence of such means would indicate evaporation of an active ingredient from the device if such had occurred.

The electrical circuit includes overriding means whereby a subject can activate the device to deliver active ingredient at other than a pre-set time up to a predetermined maximum number of such activations. For example, in patient controlled analgesia, the patient might be permitted to give himself one or two extra shots of analgesic, for example morphine, over a predetermined period of time, but any further activation of the device would be impossible until a further predetermined time period had elapsed. The electrical circuit also preferably includes a means for preventing any one electrode unit from being substituted by another electrode unit within the predetermined time period.

The current used can be in the region of 0.01-10 mA per cm^2. For example, the device most usually will operate at 0.1 to 0.7 mA, preferably around 0.5 mA. The current may be constant, variable or pulsed according to a given program of active ingredient delivery.

As indicated above, the second part may be designed so as to be thrown away after a predetermined time in a continuing treatment regimen.

When the second part of the device has a plurality of active electrodes, they can individually or collectively contain two or more active ingredients. In such an embodiment

the electrical circuit optionally includes means for activating the active electrodes containing the different active ingredients independently of each other so that they are delivered to the skin at different times.

The first part may include one power source separate from the power source associated with the second part.

Preferably the first and second parts, when in the engaged position, form a single unit, the exterior surface of which, in use, simulates the face of a time piece and said unit is attached to or mounted in a strap or bracelet for application of the device to a limb of a body. The unit will suitably include a liquid crystal display (LCD). The LCD may display current, voltage, timing and other readings as hereinbefore indicated. The unit may include an ammeter and also a voltage adjuster under the control of a control circuit. The control circuit may also include a galvanostat which keeps the current constant despite varying resistance of the skin.

In a preferred embodiment the exterior surface of the unit will resemble a wrist watch and the power source of the first part will be a long-term battery of the type which lasts for three or more years. Therefore a person undergoing a course of treatment with a device according to the invention would only have to purchase the first part of the device once for a long term course of therapy.

The or each active ingredient can be in liquid form contained in a reservoir defining part of the or each active electrode, said reservoir having an active ingredient permeable membrane forming at least part of said skin-contacting surface of said

second part of th device. Such constructions of electrode are known.

Alternatively, the active ingredient may be dispersed in a matrix of a solid, semi-solid or mucilaginous material and having an active ingredient permeable membrane associated therewith forming at least part of said skin-contacting surface of said second part of the device. The matrix material is suitably a hydrogel, polyurethane, silicone or other material known in the art for holding a drug in a stable condition prior to release to the skin.

Suitable materials for forming a matrix for use in an electrode for the device according to the invention include, for example, plant extracts, vegetable oils, gums, synthetic or natural polysaccharides, polypeptides, alginates, hydrocarbons, synthetic polymers, minerals and silicon compounds and mixtures thereof. Such materials are solidifying or gel-forming agents which upon mixing and/or heating with the active ingredient and optionally one or more auxiliary material(s) in a solvent or mixture of solvents form a matrix with the active ingredient and auxiliary material(s), if present, dispersed therethrough.

The term solidifying agent as used herein also embraces thickening, hardening, setting, suspending or like agents.

Suitable plant extracts include agar, ispaghula, psyllium, cydonia. and ceratonia or a mixture thereof. The term "agar" is synonymous with "agar-agar".

A suitable vegetable oil is hydrogenated castor oil.

Examples of suitable gums include guar gum, acacia gum, ghatti gum, karaya gum and tragacanth gum or a mixture thereof.

Suitable synthetic and natural polysaccharides include alkylcelluloses, hydroxyalkylcelluloses, cellulose eth rs, cellulos sters, nitro c llu loses, dextrin, agar, carrageenan, pectin, furcellaran and starch or starch derivatives and mixtures thereof. An example of a preferred starch derivative is sodium starch glycolate. Especially preferred polysaccharides include agar and carrageenan.

Suitable polypeptides include zein, gelatin, collagen and polygeline or a mixture thereof.

Suitable alginates include alginic acid, propylene glycol alginate and sodium alginate or a mixture thereof.

Preferred hydrocarbons include soft paraffin and hard paraffin, especially white petrolatum.

Especially preferred synthetic polyers are a carboxyvinyl polymer sold under the Trade Mark CARBOMER or a polyurethane. The polyurethanes are preferably those of the polyether type which are available commercially from The Dow Chemical Company under the Trade Name Pellethane.

Suitable minerals include bentonite, hectorite, aluminium magnesium silicate and magnesium silicate or a mixture thereof.

Suitable compounds based on silicon include colloidal silicon dioxide, silicones, polysiloxanes and silica gels or a mixture thereof.

In the case of a hydrogel the solvent used is preferably water. The solvent used may also suitably be an alcohol such as ethanol or stearyl alcohol, glycerol, propylene glycol, polyethylene glycol or silicone or a mixture thereof, including a mixture of water.

Suitable auxiliary materials may include one or more of the following: an antimicrobial agent, preservative, antioxidant, pH-controlling agent, plasticizer, surfactant, penetration enhancer, humectant, local anaesthetic, or rubefacient.

A wide range of active ingredients may be administered by means of the device according to the invention. Preferably, the active ingredient is a drug which is not normally free to pass through the skin without the assistance of an electrical current. However, even drugs which have a reasonable ability to pass through the skin without the assistance of an electrical current may benefit from being administered by means of a device in accordance with the invention, since administration by this route eliminates many of the problems associated with gastrointestinal and rectal absorption.

Suitable drugs which can be administered by means of the device in accordance with the invention include, for example, analgesics, antiasthmatic agents, antirheumatic agents, agents active on the central nervous system, peptides and hormones. Especially suitable active ingredients include fentanyl, hydromorphone, methadone, morphine, orciprenaline, salbutamol, sodium chromoglycate, diclofenac, indomethacin, piroxicam, clonidine, fluphenazine, nicotine, calcitonin, desmopressin, erythropoeitin, GH, insulin, LHRH, PTH or vasopressin or a pharmaceutically acceptable salt or ester thereof or a mixture thereof.

The device according to the invention can be used in a method of delivering an active ingredient by the iontophoretic or electro-osmotic route, which comprises applying said device to a subject to whom it is desired to administer said active ingredient.

The device may effectively vercome the need for the patient or the doctor to have any involvement with the device per se except for the possible filling of the electrode with active ingredient when an unstable active ingredient is prescribed. This is important since it is unlikely the device or method in accordance with the invention would be clearly understood by either the patient or the doctor. Accordingly, the doctor would be advised that drug X had been proven to be effective when administered for example daily on the basis of a 20 min. passage of current every 8 hours and that the electrode unit could supply seven days of treatment. For this purpose the doctor would then merely prescribe a single device and for example three months supply of electrode units for replacement on a weekly basis. The patient would then wear the device suitably like a watch so that the fact that the patient is taking medication would not be noticeable to third parties. Apart from the situations indicated above the patient's involvement would be restricted to replacing the electrode unit each week and thereafter would have no further involvement in his medication. Neither the pharmacist nor the doctor would need to do any programming to the device, since this would be done in the factory and done in such a way that the device is programmed to accept all of the electrode units that would be likely to be used in conjunction therewith. Once the program of a device has been activated by a specific electrode unit, the device would remain dedicated to that specific program. The type of program which could be accommodated in the device in accordance with the invention is essentially unlimited. Accordingly, such devices could be reprogrammed in the factory as desired to include new programs for new treatment regimens as and when they arise.

The invention will be further illustrated by the following description of embodiments thereof with reference to the accompanying drawings in which:

Figs. 1a to 1f ar schematic representations of several variants of the principl of the two-part device according to the invention;

Figs. 2 and 3 show an electric scheme of two embodiments of the two-part device according to the invention;

Fig. 4 is a sectional view of a specific example of the device in a separated state;

Fig. 5 is a partial view, in section, of the device in the assembled state;

Fig. 6 is a perspective exploded view of the two parts of the device;

Fig. 7 is a schematic representation of a two-part device for the controlled delivery of an active ingredient according to the invention;

Fig. 8 is a plan view of the second part of the device shown in Fig. 7;

Fig. 9 is a section on the line III-III in Fig. 8;

Fig. 10 is a schematic representation of an alternative construction for use as the second part of the device shown in Fig. 7; and

Fig. 11 is a circuit diagram of the circuit employed in the device according to Fig. 7.

The invention is based on a principle of which several variants are represented diagrammatically in Figs. 1a to 1f. All the elements constituting the device according to the invention

have been symbolised in these Figures, but none of them reflects the exact structure of said device. This structure is, on the other hand, represented in Figs. 4 to 10, at least in accordance with preferred embodiments.

As illustrated in Fig. 1a according to the invention, the device comprises two parts, a disposable storage and administration part 1 and a control part 2. Part 1 comprises storage means 3 for the active ingredient comprising at least one cell, and preferably several, distributed on surface 3a of said part which is to come into contact with the skin of the patient. This part also comprises at least one electrode 4 and a counter electrode 4' which, together with the skin of the patient, are designed to form a path for the iontophoretic current, these electrodes being connected to an electric circuit 5. The counter electrode preferably includes a layer of matrix material to prevent the occurrence of skin burns. The matrix material can be selected from any of those identified previously for use in the reservoir. One of the electrodes 4 is in contact with the active ingredient itself in the cell and the electrode 4 and the cell containing the active ingredient together define an active electrode 4a. The counter electrode 4' of opposite polarity is in direct contact with the skin, since it is fixed to the surface 3a, thus permitting an iontophoretic current to be created forcing the active ingredient to pass through the skin.

The two parts 1 and 2 comprise complementary means for joining them together, indicated by 6, which are so designed that they can be detached from one another again. This joining together is suitably, effected by a snap-fit connection, but other ways of joining the parts together are possible, such as a threaded joint, adhesive bonding, clamping, the use of a bayonet system, etc. as indicated above.

Part 2 comprises control means 7 comprising, in the simplest v rsion shown in Fig. 1a, a simple loop electric circuit which acts as a switch according to whether the two parts 1 and 2 are joined together or not. It would also be possible to replace this loop by a simple conductive plate or band or the equivalent.

Finally, the two parts 1 and 2 comprise mating contact means 8, 8', one provided on part 1 and the other on part 2, in order to connect the electric circuit 5 to the control means 7 when the two parts are assembled.

An important feature of the device is the fact that the energy source 9 for ensuring the iontophoresis is located in the part which is designed to act as a reservoir for the active ingredient to be administered, and is connected to the electric circuit 5.

Obviously, the amount of active ingredient that can be stored in the storage unit is necessarily limited and this unit thus has to be discarded after a certain period of time, for example, once a day. The quantity of electric energy required to administer such a dose of active ingredient is relatively high so that the energy source is also rapidly exhausted.

Accordingly, the device has the advantage of accommodating in the same part two elements that are rapidly exhausted and which necessarily render that unit disposable, whereas in the prior art one of these two elements was located in one part of the device, and the other in the other part.

The most appropriate sources of energy for supplying the iontophoretic energy are, as preferred, lithium batteries, which cause little pollution and therefore do not harm the environment despite the fact that during the course of the treatment the

patient will often us numerous storage units containing active ingredient and a batt ry, generally sp aking on such unit per day. The control part 2 which, specially in the mor detailed versions described hereinafter, is more costly, will by contrast be retained.

Finally, one of the two parts 1 or 2 comprises means, indicated by 10, designed to affix the device to the body of the patient. These means 10 are preferably a bracelet, but could equally be replaced by an elastic band, an adhesive or any other equivalent means ensuring that the device is well secured, for example, to the arm of the patient.

In a second variant of the invention illustrated in Fig. 1b, the fixing means 10 are provided on the control part 2 and the control means 7 of this part furthermore comprise a means 11 for interrupting the iontophoretic current. These means 11 comprise a switch that can be controlled from the outside by the patient himself, for example by way of a push-button, and when the switch is kept open make it possible to keep the assembled parts positioned on the body without the active ingredient being diffused. When, on the other hand, it is desired to diffuse the active ingredient the switch merely has to be closed. Consequently it is not necessary to place the device in position or remove it for each on/off sequence.

In a third variant of the invention represented in Fig. 1c, the control means 7 also comprise an electronic circuit 12 for controlling the iontophoretic current as a function of predetermined parameters P, such as the type of active ingredient, the resistivity of the patient's skin and/or the sequence of administration of the active ingredient. Indeed, it is preferable to be able to vary the voltage and/or the intensity of th- current as well as the duration and the frequency of the periods of administration according to the nature of the active

ingredient. Furthermore, the thickness of the skin and therefor the resistivity of th latter vary according to the ag of the patient and his or her race, and it is desirable to be able to adapt the current and/or the voltage supplied so as to avoid the risk of burns. The electronic circuit 12 in this case includes the switch 11 which can be controlled either by the electronic circuit or from the outside by a push-button. The electronic circuit 12 is fed by a second energy source 13, for example a button cell, represented in Fig. 1d.

Although in Fig. 1b it is imperative that the fixing means 10 are provided on the control part 2, in Figs. 1c and 1d, as well as in Figs. 1e and 1f, the means for fixing the device to the body indicated by 10 have been schematicized as forming part of the control part 2 as this is the preferred embodiment; there is no reason, however, why they should not be provided in the storage part 1.

As illustrated in Fig. 1e, the second part preferably comprises means 14 for supplying the medical parameters P to the control means and particularly to the electronic circuit 12. The supply means 14 for the said parameters are controlled from the outside by push-buttons, photoelectric or capacitive sensors or any other control means that may be found, for example, in watches.

In the variant illustrated in Fig. 1f, the supply means 14 for the medical parameters comprise encoding means 15 preferably provided on the storage part 1. The encoding means 15 may comprise at least two metallic conductors (four in the preferred embodiment) flush with the outer surface of said part and connected to the energy source 13. The conductors may be selectively broken so that each conductor represents a binary code number of which the value 1 or 0 depends on the broken or unbroken state of the conductor. Consequently, for each thus-

coded binary number there is a corresponding parameter P or group of predetermined parameters. Th encoding means 15 can be read by the decoding means 16 which are contained in the control part 2 and connected to the electronic circuit 12.

The device furthermore comprises transfer means 17 for transferring the code from one part to the other, comprising at least two metallic contacts which are provided on the control part 2 and make electrical contact with the encoding means 15 when the two parts are assembled. According to another variant, the encoding means 15 may be situated on the control part 2 and the decoding means 16 included in the storage part 1.

It would equally be possible to provide other encoding, decoding and transfer means using luminous, infra-red, magnetic or other signals, in which case the encoding means would not necessarily be connected to an energy source.

Two variants of the electrical scheme of the device according to the invention are illustrated in Figs. 2 and 3. In these Figures, the elements identical to those represented diagrammatically in Figs. 1a to 1f have the same reference numerals except that each is increased by one hundred.

As illustrated in Fig. 2, the path of the iontophoretic current commences from a terminal of the battery 109, joins the positive electrode 104 situated at the base of the reservoir 103, passes through the skin 120, the negative electrode 104', the mating contact means 108, 108', the switch means 111 provided in the electronic circuit 112, then again through the other contact means 108' towards the other terminal of the battery 109. All of these elements are interconnected by the electric circuit 105. The electrode 104 and the reservoir 103 together define the active electrode 104a.

As a variation, a second switch 121 may be provided in the electronic circuit 112 enabling th two electrodes 104, 104' to b short-circuited.

The encoding means 115 comprise metallic conductors arranged in parallel and connected by a second contact 108 to one of the terminals of the battery 113 when the two parts are assembled. The other terminal of the battery 113 is connected to the decoding means 116, then to the means 117 for transferring the code from one part to the other. When the two parts are assembled, the decoding means 116 detect the state of the conductors 115 (broken or not) through the action of the transfer means 117, and transform the code thus formed into a binary signal, which is then transferred to the electronic circuit which will act on the electric circuit 105 as a function of that code.

Fig. 3 illustrates a variant in which the switch 111 has been replaced by a commutator 122 enabling the polarity of the electrodes 104 and 104' to be reversed as a function of the ionic nature of the active ingredient employed.

Figs. 4 and 6 illustrate a preferred embodiment of the two-part device, the elements identical to those described in Figs. 1a to 1f, 2 and 3 having the same reference numerals except that each is increased by two hundred.

In Figs. 4 and 6 it may be seen that the two-part device comprises as a storage part a circular container 201 and as a control part a cover 202, also circular, which fits onto this container with a resilient snap-fit. The device thus has the general shape of a disc.

The container 201 has a base in which cells 203 are formed, open towards the outside, which house the active ingredient incorporated in a gel.

The cells are preferably circular and ar bounded by an annular flange 230.

The base of each cell is covered by an electrod 204, formed by a metallic sheet, preferably of silver or a silver-plated copper-nickel alloy known by the trade name ARCAP. The cell 203 and the metallic sheet together define the active electrode 204a. The counter electrode 204' is arranged on the base of the container so as to surround the flange 230 of each cell. As the container is preferably made of plastics material, for example ABS, the flange 230 of each cell provides insulation between the electrode 204 and the counter electrode 204' and avoids short circuits. The metallic counter electrode 204' may also be made of silver or silver-plated copper-nickel alloy.

It should be noted that the dimensions of the drawing are not to size, some of them having been notably exaggerated for greater clarity. Thus, when the device is placed on the skin, the counter electrode 204' is in direct contact with the skin.

The container 201 is formed by a body 231 in which there is provided a cavity 232 for receiving a battery 209 that provides the energy supply for the iontophoretic current. The cavity 232 is closed by a lid 233 which can be held in position adhesively, but if desired it is possible for some other fixing means to be provided.

The body 231 furthermore has a peripheral groove 234 which provides the resilient snap-fit of the cover 202, a lower lug 235 to facilitate gripping the body when the two parts 201, 202 are separated, as well as a centring collar 236 arranged around the upper surface of the container. The collar has a triangular axial section.

The cover 202 in turn has a base 237 and an annular flange 238, the whole fitting onto the container 201 and being joined thereto by means of a rib 239 which is compl mentary in section to the groove 234 of the container, the whole forming complementary joining means 206 or snap-fit means. The rib may be annular or formed by discrete lugs provided at intervals around the interior periphery of the flange 238.

The interior surface of the base 237 also has an annular recess 240 complementary in section to the centring collar 236.

The base 237 of the lid is composed of two parts 241 and 242, the latter being fixed to the former by being secured adhesively. The two parts 241 and 242 define a housing 243 in which the electronic circuit 212 and its supply battery 213 are located. The lower part 241 is provided with an opening 244 closed by a detachable lid 245 which enables the battery 213 to be replaced when it is exhausted. The lid is held in position, for example, by a bayonet fixing means, but it would also be possible to use other types of fixing means.

The upper part 242 has a sliding button 246 for controlling the switch (not shown) provided in the electronic circuit 212, and a photo-diode 247 for providing, for example, indications relating to the operation of the device or serving to indicate that one of the batteries has reached the end of its life. It would also be possible to use luminous indicators or liquid crystal displays (not shown) for these purposes.

The lower part 241 is also provided with two parallel projections 248 defining a channel for the bracelet 210. This channel terminates at each side of the part 202 in channel openings 249 represented in Fig. 6. The bracelet 210 is thus able to slide through the control part 202.

The electric circuit 205 represented in Fig. 4 according to th scheme in Figure 2 will now be d scribed.

The counter electrode 204' is connected by one of the branches of the electric circuit 205 towards the outside of the part 201 and, more exactly, terminates at the level of the centring collar 236 in such a manner as to be flush with the surface thereof and define contacts 208.

The electrode 204 arranged at the base of the cells 203 is connected to the first terminal 250 of the battery 209.

The second terminal 251 of the battery 209 is connected firstly to the centring collar 236 in order also to form an electric contact 208, and secondly, by way of four metallic conductors, to the periphery of the body 231 so as to form encoding means 215.

In the assembled state, illustrated in Fig. 5, each contact 208 touches the other contact 208' connected to the electronic circuit 212 so as to close the loop of the electric circuit 205. Moreover, the flange 238 has on its upper internal periphery four metallic contacts 217 which are connected to decoding means (not shown) provided inside the electronic circuit 212; these four contacts 217 are designed to co-operate with the encoding means 215 in the assembled state.

In addition, the battery 213 is electrically connected at 252 to the circuit 212.

In so far as the body 231 is circular and could consequently be fixed in any position relative to the flange 238, indicators (not shown) will be provided on each part 201 and 202 so that the contacts 208, 208', and 215, 217 are placed opposite each other.

A detachable protective cover 253 may also be provided on the lower surface of the part 201 to protect the active ingredient before the device is used.

Finally, by way of example, the device may have a total height of approximately 12 mm and a diameter of approximately 45 mm so that it is not very cumbersome to carry and is relatively aesthetically pleasing.

The operation and use of the device will now be explained.

As a function of the nature of the active ingredient and its desired sequence of administration, as well as the thickness and thus the resistivity of the patient's skin, on the one hand several administration programmes are determined which are memorized in the circuit 212, and on the other hand several corresponding codes are determined. During manufacture, the parts 201 are filled with active ingredient and the code is fixed by breaking or not breaking one or more contacts 215. With four contacts 215 it is thus possible to programme sixteen codes. Obviously, a higher or lower number of contacts 215 (but at least two) can be employed depending on the number of codes desired.

The part 201, preferably made of plastics material, can be of different colours according to the nature of the active ingredient, so as to facilitate use of the device by persons who are not experienced in medicine.

The patient fixes the part 202 to his or her arm by the bracelet 210 and can keep the assembly on his or her arm constantly.

When he or she wishes to change the part 201, the bracelet 210 preferably being elastic he or she will merely have to separate the part 202 from his or her arm, withdraw the old part

201 using the gripping lug 235, then position a new part 201 and reposition the assembly on his or her arm.

This technique thus makes it possible for the control part 202, which is generally costly, to be kept, and for the part 201 to be discarded after use.

Referring to Fig. 7 of the drawings, there is indicated generally at 310 a two-part device for the controlled delivery of an active ingredient to the skin under the influence of an iontophoretic or electro-osmotic force. The device 310 comprises a first part 311 housing a programmable controlling unit 312 with appropriate circuitry and an associated power supply 313, and a second part 314 having a plurality of spaced-apart active electrodes 315 arranged on a first surface 316 (Figs. 8 and 9) adapted for contact with the skin when in use. Each active electrode 315 contains an active ingredient 317 uniformly dispersed in agar gel 318. Each active electrode 315 is in the form of a well 319 with the base 320 thereof being defined by a layer of an electrically conducting material 321 which is connected to the circuitry in the first part 311 of the device 310 by a lead 322 having an associated touch button 323.

The second part 314 is releasably attachable to said first part 311 by means of a connector 324 disposed on a second surface 325 of said second part 314 remote from said first surface 316. The second surface 325 is composed of an insulating material such as a suitable plastics material. The connector 324 is engageable in a recognition position 326 on the first part 311 of the device 310. The connector 324 on engagement of the first and second parts, selects a given program applicable to said active ingredient 317 and said program when activated brings about the controlled delivery of active ingredient 317 from each said electrode 315 to the skin. Each of the wells 319 has a wall 327 of an insulating material which electrically isolates said

w lls 319 from the remainder of the first surface 316 of the s cond part 314 of the device 310. Th first surface 316 apart from the wells 319 and th walls 327 thereof is composed of an electrically conducting material such as aluminium, platinum, silver or tin which defines a counter electrode 328 connected by a lead 329 through a touch button 330 to the circuitry in the first part 311 of the device 310 and which electrode 328, when in use, allows the circuit to be completed when the device 310 is applied to the skin and is activated to deliver the active ingredient.

The programmable controlling unit 312 includes an ammeter 331, a galvanostat 332, an LCD 333 with appropriate switching arrangements which can display current, voltage and time and an audible alarm which alerts a subject when it is time for the active ingredient to be delivered, if the device is not worn continuously. The unit 312 also includes an ON/OFF button 334 for activating the program when the first and second parts are in the engaged position and an override button 335 whereby a subject can activate the device to deliver active ingredient at other than a pre-set time up to a predetermined maximum number of such activations as hereinbefore described.

An LED (light emitting diode) 336 is also provided in the unit 312 to indicate satisfactory operation of the device, for example so as to indicate that an active ingredient is being actively delivered. The LED also indicates if the power supply 313 has failed or weakened and will give an indication of the content of the active ingredient in the assembled device.

The device 310 is attached to the site of application by means of a strap 337 having at the free ends thereof the cooperating elements of a conventional clasp 338.

An alternative embodiment of a second part 314' for the device 310 is depicted in Fig. 10. The second part 314' has a

plurality of active electrodes 315' concentrically arranged on a first surface 316' adapted for contact with the skin in use. The electrodes 315' ar spaced apart from concentrically arranged rings of a metallic conducting material defining a plurality of counter electrodes 328', the latter being spaced apart from immediately adjacent electrodes 315' by a series of concentrically arranged rings of insulating material 339. In other respects, the second part 314' of the device depicted in Fig. 10 resembles the second part 314 of the device depicted in Figs. 7-9.

The main components of the circuit employed in the device 310 are depicted in the circuit diagram corresponding to Fig. 11. Said components are as follows:

PC - a programmable controlling circuit, including an audible alarm means;

PS - a power supply;

A - an ammeter;

G - a galvanostat;

SS - a selector switch;

O - an override switch

LCD - a liquid crystal display for current, voltage, time, etc. as selected; and

LED - a visible signal of delivery of active ingredient, failure of weakening of power supply, or content of active ingredient in the device 310.

RP - a recognition position.

Most of the foregoing features can be incorporated into an appropriate microchip.

It will be appreciated that the second part 314/314' of the device 310 has a separate power source associated therewith as hereinbefore described for supplying the power necessary to deliver the active ingredient to the skin in use. Thus the device 310 contains two power supplies, i.e. one associated with each of the first and second parts, and such power sources will be arranged in parallel.

CLAIMS

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1. A two-part device for the controlled delivery of an active ingredient to the skin under the influence of an iontophoretic or electro-osmotic force, comprising a reusable first part housing a programmable controlling member and an electrical circuit having overriding means whereby a subject can activate the device to deliver active ingredient at other than a pre-set time up to a predetermined maximum number of such activations, and a disposable and replaceable second part comprising an electrode unit containing said active ingredient and having at least one active electrode and a counter electrode, said at least one active electrode being disposed in, surrounded by, but isolated from, a skin-contacting surface defining said counter electrode, said second part being engageable with said first part in a manner so as to select a program applicable to said active ingredient, and said program when activated bringing about the controlled delivery of active ingredient from the electrode unit to the skin, the disposable and replaceable second part housing an associated power source for delivery of said active ingredient.

2. A device according to claim 1, wherein the first part has a power source associated with said programmable controlling member for maintaining power to said programmable controlling member.

3. A device according to claim 2, wherein said power source associated with said programmable controlling member is a long-term battery.

4. A device according to any preceding claim, wherein said at least one active electrode and said counter electrode are concentrically arranged.

5. A device according to any one of claims 1 to 4, wherein each of the first and second parts has an associated power source for delivery of said active ingredient from the electrode unit to the skin.

6. A device according to any preceding claim, wherein said at least one active electrode of the second part comprises a plurality of spaced-apart and isolated active electrodes.

7. A device according to Claim 6, wherein said active electrodes are concentrically arranged and spaced-apart by means of an insulating material.

8. A device according to any preceding claim, wherein the first and second parts have one or more co-operating electrical contact(s) which on engagement of the respective first and second parts select a given program.

9. A device according to any one of Claims 1-7, wherein the second part selects a given program by means of a bar code readable by said first part.

10. A device according to Claim 9, wherein once said second part engages said first part it is moved relative thereto enabling said bar code to be scanned by a light source in said first part.

11. A device according to any one of Claims 1-7, wherein said second part has one or more projection(s) engageable with one or more co-operating aperture(s) in said first part, the or each aperture housing a microswitch which is activated on engagement of the parts to select a given program.

12. A device according to any preceding claim, wherein the electrical circuit includes means for indicating an active ingredient is being actively delivered.

13. A device according to Claim 12, wherein the electrical circuit includes means for indicating that a power source has failed or weakened.

14. A device according to Claim 12 or 13, wherein the electrical circuit includes alarm means, where the device is not worn continuously, to alert a subject when it is time for the active ingredient to be delivered.

15. A device according to any one of Claims 12-14, wherein the electrical circuit includes means for monitoring and indicating the content of the active ingredient in the device.

16. A device according to any preceding claim, wherein the second part is adapted to be replaced after a predetermined time in a continuing treatment regimen.

17. A device according to any one of Claims 6-16, wherein the active electrodes individually or collectively contain two or more active ingredients.

18. A device according to Claim 17, wherein the electrical circuit optionally includes means for activating the active electrodes containing the different active ingredients independently of each other so that they are delivered to the skin at different times.

19. A device according to any preceding claim, wherein the first and second parts, when in the engaged position, form a single unit, the exterior surface of which, in use, simulates the face of a time piece and said unit being mounted in a strap or bracelet for attachment to a limb of a body.

20. A device according to any preceding claim, wherein the active ingredient is in liquid form contained in a reservoir defining part of the or each active electrode, said reservoir having an active ingredient permeable membrane forming at least part of said skin-contacting surface of said second part of the device.

21. A device according to any one of Claims 6-19, wherein the active ingredient is dispersed in a matrix of a solid, semi-solid or mucilaginous material and having an active ingredient permeable membrane associated therewith forming at least part of said skin-contacting surface of said second part of the device.

22. A device according to Claim 21, wherein the matrix material is a hydrogel, polyurethane or silicone material.

23. A device according to any preceding claim, wherein the first or second part includes means for activating the program when said first and second parts are in the engaged position.

24. A device according to Claim 23, wherein the means for activating the program is an ON/OFF switch.

25. A device according to Claim 24, wherein the ON/OFF switch is activated to the ON position only when the device is in situ on the body of a subject to be treated.

26. A device according to Claim 25, wherein the ON/OFF switch is activated to the ON position by pressure exerted by an attachment means when affixed to the body of said subject.

27. A device according to any preceding claim, wherein the active ingredient is selected from an analgesic, an antiasthmatic agent, an antirheumatic agent, an agent active on the central nervous system, a peptide or a hormone.

28. A device according to Claim 27, wherein the active ingredient is selected from fentanyl, hydromorphone, methadone, morphine, orcipreniline, salbutamol, sodium chromoglycate, diclofenac, indomethacin, piroxicam, clonidine, fluphenazine, nicotine, calcitonin, desmopressin, erythropoeitin, GH, insulin, LHRH, PTH or vasopressin or a pharmaceutically acceptable salt or ester thereof.

29. A device according to Claim 1, substantially as hereinbefore described with particular reference to and as illustrated in Figs. 1-6 and Figs. 7-11 of the accompanying drawings.